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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT APPLICATION EXAMINING OPERATIONS

In re the Application of	:	
Yunik Chang and Gordon Dow	:	Group Art Unit: 1623
Serial No. 10/033,835	:	Examiner: Leigh C. Maier
Filed: December 24, 2001	:	Date: July 19, 2004
For a Patent for AQUEOUS COMPOSITIONS CONTAINING METRONIDAZOLE	:	

DECLARATION OF YUNIK CHANG

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

1. I, Yunik Chang, am one of the inventors named in the present application. I am familiar with the prosecution of this application.

2. In an Office Action dated April 30, 2004, the Examiner has rejected the claims of this application under 35 U.S.C. §103(a) as being obvious in view of the prior art. Each of the rejections for obviousness is based primarily on a combination of Kata et al (Acta Pharm. Hung., 1984) and Chien et al (U.S. Patent No. 4,032,645). In order to reject some of the pending claims, the Examiner has further relied upon the disclosure of Czerneilewski (U.S. Patent No. 5,849,776) or Loftsson (U.S. Patent No. 5,324,718).

3. In Amendments filed on July 28, 2003 and on February 2, 2004, the Applicants' attorney presented arguments that (1) the Examiner had failed to establish a prima facie case of obviousness of the rejected claims based on the combination of Kata and Chien, plus or minus either Czernielewski or Loftsson, and (2) if the Examiner had established a prima facie case of obviousness, the claims of the present application are patentable because of a showing of unexpected advantageous properties as set forth in the specification.

4. In the Office Action of April 30, 2004, the Examiner rejected Applicants' showing of unexpected advantageous properties and maintained the rejection of the claims for obviousness in view of the prior art.

5. I am submitting this Declaration to rebut the Examiner's rejection of our showing of unexpected advantageous properties and to provide further evidence of such unexpected advantageous properties of the present invention. All studies described herein were performed either by me or under my supervision.

6. All solutions described below were made by mixing the components described in Example 1 of the present specification with varying concentrations of betacyclodextrin (BCD), niacinamide (NCA), and metronidazole (MTZ). BCD and NCA are solubility enhancing agents as defined in the specification on page 3, lines 21-24, which states that:

> As used herein, the term "solubility enhancing agent" or "solubility enhancer" means a chemical compound that, when present in

solution in a solvent, increases the solubility of a second chemical compound, such as an active ingredient, in the solvent, but which chemical compound is not itself a solvent for the second chemical compound.

The solutions were permitted to stand at a temperature of 5°C for at least 1 week to determine if the solutions made were physically stable. Solutions were considered to be physically stable if no precipitation or crystals were formed in the solution.

7. As disclosed in the present specification, on page 15, lines 9-10, the stable solubility of MTZ in aqueous gel solution (without either BCD or NCA) at 5°C is 0.7%. It is noted that, according to the definition in the specification and in paragraph 6 above, water is not a solubility enhancing agent for MTZ. Rather it is a solvent for MTZ. The 0.7% inherent solubility of MTZ in aqueous gel solution is also disclosed in Example 1, at column 6, line 45, of Chang, U.S. Patent No. 6,468,989. I am a co-inventor of the Chang patent.

8. As disclosed in the present specification in Example 1 on pages 11 and 12, the concentration of a saturated physically stable solution of BCD in the aqueous gel fluid at 5°C is shown in Table 1 to be 0.5% w/w.

9. As disclosed in the present specification in Example 2 on page 12, the maximum stable solubility of MTZ in the aqueous gel containing 0.5% BCD is 0.8% w/w. Thus, the addition of 0.5% BCD to aqueous gel fluid results in an increased

solubility of MTZ of 0.1% w/w compared to the inherent solubility (0.7%) of MTZ in the aqueous gel fluid without the solubility enhancer, BCD.

10. In a study recently conducted following the issuance of the present Office Action, the stable solubility of MTZ at 5°C was determined for aqueous gel fluid containing 1.0% NCA. Five vials of each solution were prepared and the presence of crystals of precipitates was determined following one week storage at 5°C. The data is summarized in Table 1.

NCA Concentration % w/w	MTZ Concentration % w/w	Results, 5°C, 1 week
1.0	0.5	Clear
1.0	0.6	Clear
1.0	0.7	Clear
1.0	0.8	Mostly clear
1.0	0.9	Crystals formed

Table 1

11. The data of Table 1 and the disclosure in Chang, US Patent No. 6,468,989 at column 10, lines 44-46 that a 3% niacinamide concentration is required to obtain a 1% metronidazole aqueous solution is consistent with the disclosure of Chien, J. Parenteral Science and Technology, 38(1):32-36 (1984) that "the aqueous solubility of metronidazole increases linearly as increasing the concentration of nicotinamide[1] in the aqueous solution." See page 35, column 2, lines 1 and 2. Thus, based on the finding in Chang that a 3% NCA concentration is required to provide an increase in aqueous

[1] The terms "niacinamide" and "nicotinamide" are synonymous and refer to the same chemical compound.

solubility of MTZ of 0.3% over the inherent aqueous solubility in water without NCA, one would expect a 1% NCA concentration to provide an enhancement of solubility of 0.1% over the inherent aqueous solubility of MTZ. This expected result is the result that was obtained in our study.

12. The above data establish that a 0.5% concentration of BCD provides an enhancement in MTZ aqueous solubility of 0.1% w/w and that a 1.0% concentration of NCA provides an enhancement in MTZ aqueous solubility of 0.1% w/w. Thus, if the enhancement in MTZ aqueous solubility of the combination of 0.5% BCD and 1.0% NCA were additive, one would expect the combination to provide an enhancement of MTZ aqueous solubility of 0.2% (0.1% due to BCD + 0.1% due to NCA) above the inherent aqueous solubility of MTZ, or a solubility of 0.9% w/w.

13. However, as disclosed in the present specification in Example 3, in Table 4, on page 13, the combination of 0.5% BCD and 1.0% NCA provides a stable MTZ aqueous solution of 1.0% w/w, for a total solubility enhancement, not of 0.2% as would be expected if BCD and NCA acted additively, but of 0.3%, which is 50% higher than this expected solubility enhancement. This data establishes synergy of MTZ solubility enhancement by the combination of BCD and NCA in aqueous fluid.

14. Although the above data clearly establishes synergy, the synergistic activity of BCD and NCA were further studied as follows.

15. The present specification, in Example 3, Table 4, on page 13, discloses that an aqueous solution containing 0.5% BCD, 0.5% NCA, and 1.0% MTZ resulted in crystal formation after 1 week of storage at 5°C, indicating that the solution was not stable and that crystals came out of solution. Table 4 further discloses that at a concentration of 1.0% BCD, 0.5%, NCA, and 1.0% MTZ, a precipitate (non-crystalline) was formed, indicating limited solubilization of BCD and/or MTZ. This is expected due to the fact that the maximum aqueous solubility of BCD at 5°C is 0.5% w/w and due to the fact that the minimum NCA concentration required to raise the solubility of BCD to 1.0% is higher than 0.5%.

16. However, the data in Table 4 further discloses that a solution of 1.0% BCD, 1.0% NCA, and 1.0% MTZ was physically stable at 5°C. No crystals of MTZ and no precipitate of BCD were formed. Based on the data shown in Table 4 that a 0.5% BCD, 1.0% NCA, and 1.0% MTZ solution was stable, it would be expected that the MTZ would remain in solution when additional BCD (1.0%) was present in the solution. What is surprising from this data is that, when combined with 1.0% NCA, the 1.0% BCD remained in solution and did not form a precipitate. That is, the aqueous solubility of BCD was at least doubled when combined with 1.0% NCA.

17. To determine how much the solubility of MTZ in aqueous fluid is increased when combined with 1% NCA and 1% BCD, aqueous gel solutions as in Example 1 of the specification were prepared as described above and in the specification with a concentration of 1.0% w/w of each of NCA and BCD and varying concentrations

of MTZ. Five vials of each solution were prepared and the presence of crystals of precipitates was determined following one week storage at 5°C. The results are summarized in Table 2.

NCA Conc. % w/w	BCD Conc. % w/w	MTZ Conc. % w/w	Results, 5°C, 1 week
1.0	1.0	0.9	Clear
1.0	1.0	1.0	Clear
1.0	1.0	1.1	Clear
1.0	1.0	1.2	Light crystal formation
1.0	1.0	1.3	Heavy crystal formation

Table 2

18. The data in Table 4 of the specification and in Table 2 above provide further insight into the synergistic activity of the combination of BCD and NCA. The data establish that the combination of NCA in aqueous fluid with BCD increases the dissolved concentration of BCD to a level significantly greater than could be obtained without the NCA. Additionally, the higher concentration of BCD thus obtained, together with the NCA, provide for much greater dissolved concentrations of MTZ that would otherwise be obtainable. As shown in Table 2 above, a combination of each of 1.0% NCA and 1.0% BCD in aqueous gel fluid provides a stable dissolved concentration of MTZ of 1.1%. Such data is clearly an indication of synergy because, without the NCA, a level of 1.0% BCD at 5°C is unobtainable. It is only when the two are combined can such high dissolved levels of BCD and MTZ be obtained.

19. Although not essential to the substance of this Declaration or to establish the synergistic activity of the combination of BCD and NCA, I am providing a proposed

mechanism for the synergistic activity of BCD and NCA. I conjecture that when NCA and BCD are combined in an aqueous fluid, these two compounds form a complex. The increased aqueous solubility of BCD when combined with NCA strongly suggests the formation of such a complex. The formation of this complex provides a rationale for the increased solubility of BCD in aqueous fluid when combined with NCA and for the synergistic activity of the combination of BCD and NCA.

The formation of a complex of NCA and BCD that results in increased solubility of BCD in aqueous solution is itself surprising. BCD is a very large molecule with a molecular weight of about 1135. NCA is a much smaller molecule with a molecular weight of about 122. It is surprising that, by adding the small NCA molecule to an aqueous solution of BCD, a complex of NCA and BCD would be formed that would cause increased amounts of BCD to be dissolved. Such interactions are known in the art to increase the solubility of a smaller molecule by combining with a larger molecule but, to my knowledge, such an interaction whereby a small molecule complexes with a larger molecule to increase solubility of the larger molecule is not known and has neither been reported or even speculated on previously.

I hereby declare that all that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001

of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Yunik Chang

7-19-04

Date